

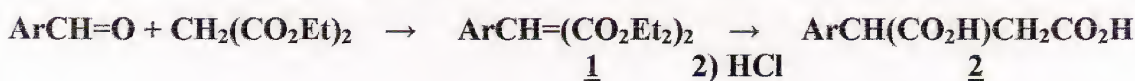
# A FACILE GENERAL SYNTHESIS OF ARYLMALEIC ANHYDRIDES.

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By a sequence involving Knoevenagel condensation, Michael addition of cyanide, hydrolysis, and selenium dioxide oxidation, a series of seven aryl maleic anhydrides were prepared in excellent overall yields. The regiospecificity of reaction of these anhydrides with various nucleophilic species, e.g.  $\text{Me}_3\text{SiN}_3$ ,  $\text{NH}_3$ , and  $\text{PhNH}_2$  was investigated. Except for a few cases, the nucleophile attacks the more hindered carbonyl, in a reaction controlled by electronic rather than steric factors. These anhydrides are of particular utility in the synthesis of 4- and 5-Aryl Substituted 1,3(3H) Oxazine-2,6-Diones (Oxauracils)<sup>1,2</sup>.

Piperidine

1) KCN



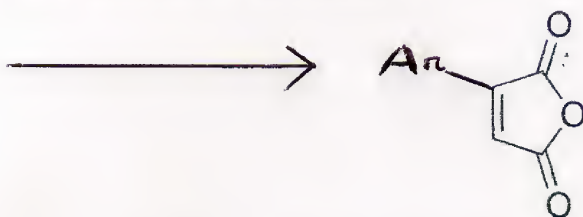
2a, Ar= Ph, 2b, Ar= p-F,

2c, Ar=pOMe, 2d, Ar= p-Br,

2e, Ar=3-Cl-4-Me, 2f, Ar= o-Cl ,

2g, Ar= 3,4-diCl

2a-e,  $\text{SeO}_2$ /acetic anhydride



3a, Ar= Ph, 3b, Ar= p-F, 3c Ar = pOMe, 3d, Ar= p-Br,

3e, Ar= 3-Cl-4-Methyl, 3f, Ar= o-Cl, 3g, Ar= 3,4-diCl

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## Experimental

### Phenyl Maleic Anhydride (3a)

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 14.7 g (0.076 mol) phenyl succinic acid (2a), 8.3 g (0.075 mol) selenium dioxide, and 60 ml acetic anhydride. The solution was heated at reflux for 6 hours and filtered hot through a sintered glass Buchner funnel. Concentration of the filtrate on a rotovap gave an orange solid. The solid was boiled with 150 ml diethyl ether for one hour, then again suction filtered, yielding 9.8 g (73.7%) phenylmaleic anhydride, 3a, mp 118-22°, (Lit<sup>3</sup> mp 119-199.5°C).

### p-Fluorophenyl Maleic Anhydride (3b)

A 100ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 3.3 g (0.0156 mol) p-fluoro phenyl succinic acid (2b), 1.9 g (0.0171 mol) selenium dioxide and 40 ml acetic anhydride. Mixture was refluxed for 24 hrs and worked up as in 3a above, yielding 1.8g (60%) of 3b, tan crystals, mp 111-114°C).

IR (CDCl<sub>3</sub>) 3140(w), 1860(m), 1840(m), 1810(m), 1770(vs), 1620(m), 1600(s), 1505(s), 1415(w), 1310(m), 1300(m), 1290(w), 1225(vs), 1160(s), 1090(m), 1050(m), 1005(w), 830(s), 800(m) cm<sup>-1</sup>.

Nmr (60 Mhz, DMSO-D<sub>6</sub> Delta ), 8.1 (d of d, 2H, meta to F, J<sub>om</sub>= 10Hz, J<sub>oF</sub>= 5Hz), 7.55 (s, 1H, olefinic), 7.26(t, 2H, ortho to F, J<sub>om</sub>=J<sub>oF</sub> = 10Hz).

### p-Methoxyphenyl (Anisyl) Maleic Anhydride (3c)

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 33.5 g (0.150 mol) p-Methoxyphenyl succinic acid, 2c, 19.4 g, (0.150 mol) selenium dioxide, and 125 ml acetic anhydride. The solution was heated for 21 hours and filtered hot through a sintered glass funnel. The filtrate was concentrated on the rotovap yielding brown semisolids, which were titrated with hexane then ether, then hot CCl<sub>4</sub>, yielding 9.3 g (43.2%) 3c, mp 140-143°C, (Lit<sup>3</sup> mp 142.5-143.5°C).

Nmr (60 Mhz, DMSO-D<sub>6</sub>), delta 3.9 (s, 3H, OCH<sub>3</sub>), 7.1 (d, J= 9Hz, 2H, Aromatics), 8.1 (d, J= 9Hz, 2H, Aromatics), 7.5 (s, 1H, olefinic).

### p-Bromo Phenyl Maleic Anhydride (3d)

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 8.0 g(0.0293 mol) 3-bromophenyl succinic acid (2d), 3.5 g( 0.0310 mol) selenium dioxide and 70 ml acetic anhydride. The mixture was refluxed for 22 hrs and worked up by concentrating to 40 ml on a rotovap, cooling, and washing with 50/50 ether/hexane. Vacuum drying gave 4.75 g (64.2%) 3d, mp 152-154°C, tan crystals.

IR (CDCl<sub>3</sub>), 1860(m), 1820(m), 1800(m), 1775(vs), 1620(m), 1405(m), 1320(w), 1300(w), 1250(w), 1230(w), 1185(w), 1160(w), 1090(m), 1070(m), 1050(m), 1005(m), 820(s) cm<sup>-1</sup>.

### 3-Chloro-4-Methyl Phenyl Maleic Anhydride (3e)

A 250ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 7.5g(0.031 mol) 3-chloro-4-methyl succinic acid, 2e, and 100 ml acetic anhydride. Mixture was refluxed for 22 hrs and worked up as in 3a above, yielding 4.3 g (62.3%) 3e, mp 98-102°C.

IR (CDCl<sub>3</sub>) 3070(w), 2990(w), 1840(m), 1770(s), 1610(m), 1550(w), 1490(m), 1310(m), 1290(m), 1270(m), 1220(s), 1150(w), 1080(m), 1060(m), 1040(m), 980(m), 810(m) cm<sup>-1</sup>.

Nmr (60 Mhz, DMSO-D<sub>6</sub> Delta ), 7.95(d, 1H, aromatic, Jo-o<sup>1</sup> = 2Hz), ), 7.75 (d of d, 1H, H ortho, Jom = 8Hz, Jo-o<sup>1</sup> = 2Hz), 7.40 (d, 1H, Hm, Jom= 8Hz), 7.05(s, 1H, olefinic), 2.50 (s, 3H, methyl).

### Chlorophenyl Maleic Anhydride (3f)

A 300 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 15.6 g (0.069 mol) o-chlorophenyl succinic acid (2f), 8.3 g (0.075 mol) selenium dioxide and 60 ml acetic anhydride. The mixture was refluxed for 8 hours. The acetic anhydride was removed on a rotovap, yielding a dark brown oil, which was taken up in 15 ml benzene and cooled to room temperature. 5 ml cyclohexane was added and the solution cooled in an ice chest, yielding 9.9 g (70.2 %) 3f, mp 64-5°C, (Lit<sup>3</sup> mp 68-9°C).

### 3,4-Dichlorophenyl Maleic Anhydride (3g)

A 250 ml round bottom flask with heating mantel, magnetic stirrer and water condenser was charged with 32.2 g (0.122 mol) 3,4-dichloro phenyl succinic acid (2g), 14.7 g (0.1325 mol) selenium dioxide and 130 ml acetic anhydride. The mixture was refluxed for 20 hrs and worked up as in 3a above, yielding 22.8 g (77%) 3g, mp 110 –115°C, (lit<sup>2</sup>, mp 115-116°C).

IR (CDCl<sub>3</sub>) 3120(w), 1840(m), 1770(vs). 1620(m), 1590(w), 1300(w) 1250(w), 1220(s), 1130(m), 1080(m), 1050 (m), 1020 (m). 980(m), 810(m) cm<sup>-1</sup>

NMR (60 Mhz, CDCl<sub>3</sub>), delta 7.71 (m, 3H, aromatics), 7.0(s, 1H, olefinic).

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- 2) J.H. MacMillan and S.S. Washburne "Further Investigation of the Interaction of Trimethylsilyl Azide with Substituted Maleic Anhydrides, Synthesis of 4-and 5-Aryl Substituted 1,3(3H) Oxazine-2,6-Diones" J.Heterocyclic Chemistry Vol. 12, p1215 (1975).
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